DRAFT – 05.12.00

CAUSATION

Summary:

We apply Rothman's general model for defining causation (Rothman & Greenland 1997)* to describe the relationship of smoking to a number of health endpoints. The basis of this model is described in detail below, but can be summarised by defining "cause" to be any event, condition or characteristic which is present prior to the disease developing and is necessary for the disease to occur. Most, if not all, diseases require a number of such causes, or "risk factors", to be present. Thus each contributing causal factor is often referred to as a "component cause". A combination of such component causes which is complete enough to result in a specific disease is defined as a "sufficient cause" for that disease (e.g. as discussed in Beaglehole et al. 1993; Rothman & Poole 1996,).

Ultimate proof of direct causation is often, if not always, elusive. However evidence can be accumulated from a number of fields in support of such relationships. We discuss below the extent and nature of the evidence required to support different actions in different contexts with respect to smoking and health. For example, based on epidemiology (and other supportive evidence), it seems likely that "smoking" is a "component cause" for a number of health endpoints including lung cancer, chronic obstructive pulmonary disease (COPD) and cardiovascular disease. From the point of view of the public health community this evidence is sufficient to support the conclusion that reduction of smoking would result in a decline in incidence of these diseases.

However, for those adults who choose to continue to smoke, health benefits may be effectively achieved by providing them with products which are intrinsically less harmful. The design of such reduced harm products requires a more technical, mechanistic understanding of 'how' the current cigarettes act with respect to different health endpoints. Although many promising avenues are suggested by mechanistic evidence to-date, there are still many gaps in our knowledge in this area. Some of these gaps and proposals for how to fill them are also discussed below.

Introduction:

"Cigarette Smoking and Disease in Smokers: We agree with the overwhelming medical and scientific consensus that cigarette smoking causes lung cancer, heart disease, emphysema and other serious diseases in smokers. Smokers are far more likely to develop serious diseases, like lung cancer, than non-smokers. There is no "safe" cigarette. These are and have been the messages of public health authorities worldwide. Smokers and potential smokers should rely on these messages in making all smoking-related decisions."

This is the statement on smoking and health that is found on the current PM website. Although this statement is unquestionably consistent with our current scientific understanding of smoking and disease, it is too brief to capture both the complexities of this relationship as well as to identify gaps in basic understanding. In addition, of particular importance is the question, what exactly does the term "cause" mean, in this context, and what are the appropriate criteria to apply to the available evidence in order to determine if it is consistent with a causal relationship?

The purpose of this document is to describe the current view of PM scientists on this issue. It is not intended to fully review all the evidence on any particular disease, but rather to establish the reasoning behind PM scientists' conclusions regarding the understanding of causation. The considered opinions of the

* Note: Please see p7 for further comments on this Rothman and Greenland paper.

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company scientists responsible for evaluating the evidence in this field have evolved over time, and will, inevitably, continue to evolve as new information becomes available.

Concepts of Causality:

It is an innate part of human nature to seek causal explanations for relationships. It is the understanding of such causal relationships that form our view of the world in which we live. In the most general terms this helps each individual to determine which actions result in which effects. More fundamentally we should be asking ourselves why we want to determine causal associations. Surely the answer to this question is that we wish, somehow, to take action to optimise the situation with respect to the relationship. If we knew that a given activity "causes" a desirable effect, we would presumably wish to take action to maximise the desirable effect.

The level of "proof", or of understanding, of any such relationship is largely dictated by the results that we wish to achieve. For the most part the relationships that people deal with are extremely simple, and in many cases were first encountered during childhood. Often the causal component is not even considered. Thus, children learn from an early age that certain "actions", such as pressing a light switch, result in certain "effects", such as illumination. For most children the evidence provided by repeated successful 'experiments' will be entirely satisfactory for them to learn how to switch on a light. They are not generally concerned with the detailed mechanics connecting the light switch to the bulb. Nor are they generally perturbed by the occasional failure of the experiment – such as when the light bulb is not functioning.

Many such associations, however, are not so clear cut. An infant, for example, will exert the "action" of crying when in need of attention. The "cause" of the infant's dissatisfaction, however, may not be that apparent to the carer of the infant, frequently resulting in a flurry of activities designed to satisfy the vaguely expressed requirements of the infant!

Seeking causal explanations of health endpoints usually focuses on identifying particular conditions that are associated with an adverse health endpoint. In order to optimise the situation in this context, we would presumably wish to take action to reduce the adverse health effects.

Historically we can identify discussions of causation in human disease since the very earliest beginnings of medicine. For the past several centuries the development of studies of diseases within populations, i.e. epidemiology, has sought to identify possible underlying causes of these diseases in search of directions resulting in either cure or prevention. In parallel with such studies, however, the definition or concept of causation per se has undergone rigorous debate. Already in the 18th century Hume argued that all knowledge was based on our own subjective view of the world, and therefore causality could never be undisputedly proven. Kant argued against Hume's view, proposing that a key *synthetic a priori* judgement was that events had causes, and that the role of science was to identify these causes by the process of induction, (See for example Susser 1991; Rothman and Poole 1996, for discussions on concepts of causation). It is important to note that the concept of causation is complex. It is virtually meaningless to state that "A" causes "B", without clearly defining what is meant by the term "cause" and the context within which it is being used. This is the subject of this document.

The concepts that will thus be explored in this document are: a general definition of causation; causal inference in epidemiology (i.e. the judicial assessment of the evidence); and the interpretation of evidence relating smoking to various health endpoints in different contexts – particularly in relation to the actions available to reduce these adverse health effects.

A General Definition of Causation:

One of the simplest concepts of causation relevant to the field of medicine is that described by Koch's postulates, – which, paraphrased, suggest that an agent is causal if it is both necessary and sufficient to cause the disease in question. Koch's postulates apply reasonably well to infectious diseases, particularly where the infectious agent defines the disease, although over the years Koch himself expanded these principles to include factors such as susceptibility to infection (for discussion see Carter 1985). They are clearly not satisfactory for many multi-factorial or chronic diseases. It is also clearly the case that smoking is neither necessary (as lung cancer is not restricted only to smokers) or sufficient (as many smokers will never contract lung cancer) in its own right for lung cancer to occur. Thus, smoking would not satisfy a simple

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'necessary & sufficient' definition of causation. This is, however, probably not an appropriate (or a particularly meaningful) model for causation in this context.

A more pragmatic and general model would consider the potential for modifying 'risk' of an undesirable event through alteration of another contributory factor. Such a definition was applied by the US Surgeons General in their reviews. In fact, in the first Surgeon General's report the following comment was made about the use of the term "cause":

> "*The word cause is the one in general usage in connection with matters considered in this study, and it is capable of conveying the notion of a significant, effectual, relationship between an agent and an associated disorder or disease in the host." .."It should be said at once, however that no member of this Committee used the word "cause" in an absolute sense in the area of this study."* (U.S. Department of Health Education and Welfare 1964).

In terms of the probable causal relationship between smoking and a number of health endpoints, we consider the model outlined by Rothman & Greenland to be the one that most closely fits the evidence currently available (Rothman and Greenland 1997). This is also a model that appears to have widespread acceptance in the public health and epidemiological community (e.g. as referenced by Beaglehole et al. 1993, and in; Detels et al. 1997).

In order to explore this model further, and to examine how it might apply in the smoking and health context, we first need to define some of the terms used:

"CAUSE"	*"an antecedent event, condition, or characteristic that was necessary for the occurrence of the disease at the moment it occurred, given that other conditions are fixed."* Note that in this definition it may be that no specific event, condition, or characteristic is sufficient by itself to produce the disease. This definition, therefore, only defines a "component cause" and not the complete causal mechanism.
"SUFFICIENT CAUSE"	*"a set of minimal conditions and events that inevitably produce disease."*
"COMPONENT CAUSE"	One element of a "sufficient cause". Note that for many diseases, most of the individual "component causes" are unknown.
"RISK FACTOR"	The term "risk factor" is commonly used to describe factors that are associated with a disease endpoint but are not themselves sufficient to cause the disease. In most contexts this term is interchangeable with that of "component cause".
"NECESSARY CAUSE"	A "component cause" that is essential for the development of the disease. In other words, a "necessary cause" must act as one of the "component causes" **in all** of the complete minimal sets constituting the "sufficient causes" for that disease.

It is important to note that there may be several different combinations of "component causes" for any given disease, and it is extremely rare for any disease to be caused by just one single component. For example, it may be believed that the only "component cause" necessary for the development of tuberculosis would be infection by the tuberculosis bacillus. However, in fact, in addition to the requirement of infection the individual must also lack immunity to this infection for tuberculosis to occur. In fact, the bacillus is a "necessary cause" for tuberculosis, (in that the disease cannot develop in its absence); however, it is not in itself a "sufficient cause". (Rothman 1976; Beaglehole et al. 1993; Rothman and Greenland 1997).

It should also be noted that it might not be necessary to identify all components of a "sufficient cause" before effective prevention can take place. The removal of one component will prevent the development of the disease due to the fact that this "component cause" is a necessary component for a "sufficient cause". However, there may be other "sufficient causes" which do not require this component, and thus the disease could still develop through a different route, although perhaps at a different time.

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The model of Rothman and Greenland is best described with the aid of the diagram in Figure 1. In this diagram the three circles represent three "sufficient causes" for a disease. A, B, C, D and E are "component causes" of the "sufficient cause I". Likewise A, B, F, G and H are "component causes" for the "sufficient cause II", and A, C, F, I and J for "sufficient cause III". Assuming that these are the only "sufficient causes" for the hypothetical disease, "component cause A" can be considered a "necessary cause", in that the disease will never occur if this is not present. Thus, eliminating "component cause A" would effectively eliminate the disease. Elimination of any of the other components would only reduce the incidence of the disease by eliminating the "sufficient cause" of which the "component cause" is a factor. Thus, elimination of B would effectively prevent the disease caused by "sufficient causes I and II", but would have no effect on the disease caused by "sufficient cause III".

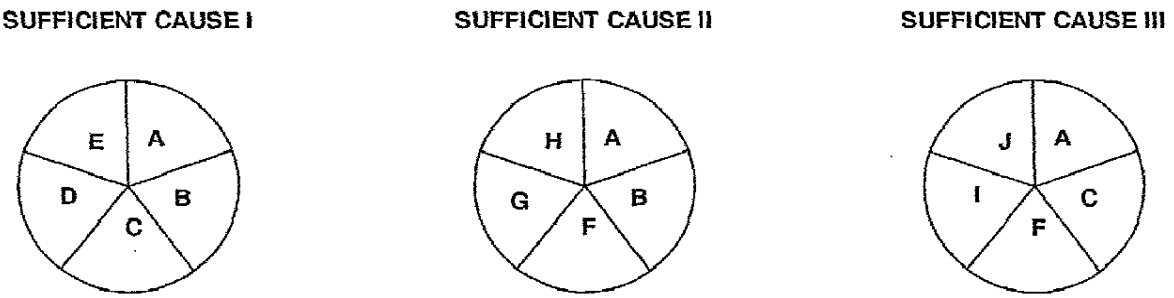

Figure 1: Conceptual scheme for the causes of a hypothetical disease (Rothman and Greenland 1997)

It is illuminating to consider this model in respect of the evidence relating smoking to lung cancer. Smoking can be considered a "component cause" for lung cancer. It may play such a causal role in more that one combination of components, (i.e. more than one "sufficient cause"), but it clearly does not make up a "sufficient cause" in its own right, as most individuals who smoke do not contract lung cancer. Neither is it a "necessary cause", because some non-smokers will contract lung cancer. Therefore there must be some combination of "component causes" sufficient to cause lung cancer that does not include smoking as a component.

From the definition above it may be possible to suggest that for a general population the incidence of a particular disease would not be so high in the absence of smoking and therefore smoking could be considered "causal" for this disease in this population. It is, however, on the basis of current evidence, virtually impossible to determine whether a disease in an individual smoker would have developed in the absence of smoking. Lack of ability to determine this makes it impossible to determine the exact causal role of smoking in any one individual.

Causal Inference in Epidemiology:

Investigators interested in determining the possible causes – whether "component", "sufficient", or "necessary" – do not always have the luxury of using the above analysis, since it is often the fact that knowledge is insufficient to identify causes with any certainty. In such cases "causal inference" is frequently utilised. Causal inference refers to the application of scientific judgement to determine whether the evidence available supports the determination of a causal relationship between a factor and a health effect.

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In the public health arena, particularly in the area of smoking and health, epidemiological evidence is extensively drawn upon to determine causal relationships. For the most part this is either because epidemiological evidence is all that is available, or at least provides the first indications of potentially causal relationships. However, epidemiological studies can never provide the 'ultimate proof' of a causal relationship. Indeed, interpreting epidemiological evidence of necessity requires the application of judgement.

In the first instance elements involved in the design and execution of an epidemiological study have to be considered to draw a judgement as to whether a real association is apparent between the factors under investigation. Even given that such an association is established, further judgement is necessary to determine whether such an association could be seen as causal, and whether it is generalisable to other populations. The first judgement (i.e. that of an association) is largely statistical in nature and can be determined by the prudent application of appropriate statistical methods. The latter, that of causal inference, goes beyond any statistical association. Indeed, this was clearly recognised in the first report of the US Surgeon General in 1964:

> *"Statistical methods cannot establish proof of a causal relationship in an association. The causal significance of an association is a matter of judgment which goes beyond any statement of statistical probability. To judge or evaluate causal significance of the association between the attribute or agent and the disease, or effect upon health, a number of criteria must be utilized, no one of which is an all-sufficient basis for judgment."* (U.S. Department of Health Education and Welfare 1964)

In addressing this step many proposals for "criteria for judgement" have been discussed, the earliest examples stemming from this first report of the US Surgeon General, and the famous Bradford Hill "criteria" (U.S. Department of Health Education and Welfare 1964; Hill 1965). In fact it should be noted that Sir Austin Bradford Hill never discussed these as "criteria", but rather as "aspects of an association" that should be considered before deciding that the most likely interpretation of the association is causal.

The US Surgeon General's first report in 1964 outlined five criteria as follows:

a. the consistency of the association
b. the strength of the association
c. the specificity of the association
d. the temporal relationship of the association
e. the coherence of the association

Sir Austin Bradford Hill listed 9 aspects of an association for consideration:

1. Strength
2. Consistency
3. Specificity
4. Temporality
5. Biological gradient
6. Plausibility
7. Coherence
8. Experiment
9. Analogy

It can be seen from the above lists that all five of the Surgeon General's criteria are covered by Hill's aspects approach, although it would appear that Hill has included four additional criteria. Scrutiny of the explanations of these different aspects reveals considerably more overlap than may first appear.

Strength

Hill argues that a strong association is much more likely to be due to a causal relationship than a weak one. As examples he cites the association noted between having an occupation as a chimney sweep and scrotal cancer, as identified by Percival Pott, and the more modern example of lung cancer in cigarette smokers. For both of these he suggests that the strength of the association is so large that it is difficult to imagine any other environmental influence which could explain an association of such magnitude. On the other hand he points out that the death rate from coronary thrombosis in smokers is only twice that of non-smokers, and it is easier to suggest alternative features of life that may go hand-in-hand with smoking which may be the underlying cause of the

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thrombosis. Hill is careful to note, however, that even weak associations may be the result of causal relationships and should not simply be dismissed.

The US Surgeon General's report similarly discusses the relative risk estimates as a measure of the size of the effect of a factor on a disease. The criteria of strength was considered satisfied if the size of the resulting relative risk was sufficiently large to suggest that even in the presence of another agent, without causal effect, but correlated with the causal agent, the effect would not be obscured by the presence of the non-causal agent.

Thus both the US Surgeon General's report and Hill suggest that 'strong' associations are unlikely to have been observed due to bias or confounding.

Consistency

For both Hill and the US Surgeon General's report evaluation of studies that repeatedly show similar effects under different conditions, (different by design, population, circumstances and time) supports a causal interpretation of such effects. Hill is careful to point out that in some circumstances a single study may be sufficient to indicate a cause-effect relationship.

Specificity

The definition of specificity in the context of epidemiology clearly presents some problems to Hill. Similar problems are also reflected in the discussion from the US Surgeon General's report. Both recognise that it is extremely rare that a single agent invariably predicts the occurrence of a single disease, and likewise since most diseases may have multiple causes (a concept that is further defined by the Rothman and Greenland model, 1997). Both Hill and the US Surgeon General's report argue that specificity may present itself in the form of the magnitude of the association – both citing the association of smoking with lung cancer as the example. Hill concludes by stating that *"if specificity exists we may be able to draw conclusions without hesitation; if it is not apparent, we are not thereby necessarily left sitting irresolutely on the fence".*

Temporality

It has been argued by some that this criterion, although not in itself sufficient, is the only one that absolutely has to be satisfied to conclude a causal relationship (Weed 1997). However, both Hill and the US Surgeon General's report point out that for chronic diseases it is not always possible to demonstrate that this has occurred (and it is by definition never possible by case-control studies). Thus, although logically it would seem necessary to establish that the causal agent preceded onset of the disease, in reality this may not be definitively demonstrable. It is, however, evident that if the inverse is proven, (i.e. that the disease pre-dated the exposure), then a causal association could be dismissed.

Biological gradient

Hill and the US Surgeon General's report suggest that establishing a dose-response effect strengthens the evidence of a causal relationship. The US Surgeon General considers this in their discussion on strength and coherence, whereas Hill specifies it as an independent characteristic. Once again, however, Hill notes that absence of a dose-response relationship does not disprove causality. The lack of a dose-response relationship may sometimes be accounted for by a more complex explanation. In addition lack of satisfactory quantitative measures of exposure in epidemiological studies may often obscure any dose-response relationship.

Plausibility

In fact, neither Hill nor the US Surgeon General's report discusses biological plausibility to any great extent. Hill refers to a biologically plausible explanation as being very helpful. He points out, however, that one's ability to determine such an explanation is evidently limited by the biological knowledge of the day. Absence of a biologically plausible model thus cannot be taken as supporting a non-causal explanation.

The US Surgeon General's report does not discuss biological plausibility in relation to epidemiological evidence. They do, however, consider evidence other than epidemiology in drawing

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conclusions about causality. The biological plausibility of an association, according to the US Surgeon General's report, is considered important, but not essential, in causal inference.

Coherence

Both Hill and the US Surgeon General's report consider coherence as an important criterion for evaluation. As Hill describes it, the *"cause-and-effect interpretation of our data should not seriously conflict with the generally known facts of the natural history and biology of the disease".*

Experiment

Hill's view of experimental evidence is evidence that preventive action based on the causal hypothesis results in a reduced frequency of the associated disease. Although Hill is careful to point out that such evidence is not always available, he notes that such evidence, when present, may present the strongest support for the causal hypothesis. Although the US Surgeon General's report does not refer directly to such experimental evidence, they do refer to evidence based on lowered risks following discontinuance of smoking as presenting some of the strongest evidence for the coherence of the association.

Analogy

Hill's view on analogy is that in some circumstances, prior experience in similar circumstances may contribute to the decision on a causal association. Thus he suggests that the knowledge on the effects of thalidomide and rubella during pregnancy may make it easier to accept slighter, but similar evidence for another drug or viral disease in pregnancy. The US Surgeon General's report does not discuss analogy per se.

Some authors, including Rothman and Greenland (1997), have challenged the validity of such criteria. It is our view, however, that such 'criteria' provide considerable guidance in maintaining consistency in evaluating epidemiological evidence, provided that one continually bears in mind that no single criterion should be considered essential or sufficient to prove a case. In fact both of these publications, which first described this approach, were careful to point out that these criteria are only guidelines for judgement. The US Surgeon General's report states that no one criterion is a sufficient basis for judgement. Sir Bradford Hill echoes this sentiment by stating:

> *"What I do not believe – and this has been suggested – is that we can usefully lay down some hard-and-fast rules of evidence that must be obeyed before we accept cause and effect. None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a sine qua non."*

Since the early 1960s both Hill's paper and the US Surgeon General's report have frequently been cited in reviews which purport to apply their 'criteria' to numerous different sets of evidence. A synopsis of such reviews reveals that the rigidity with which such causal 'criteria' are applied is very variable, and often reasons for inclusion or exclusion of specific criteria are not critically evaluated (Weed & Gorelic 1996). Arguably this is not inconsistent with the original authors' intentions. It does, however, emphasise the role that judgement plays in causal inference.

In addition, scientific knowledge has considerably changed since these criteria were first discussed. It has been argued that the application of such criteria should similarly advance. Most notably, there appears to be more emphasis in recent years on biological plausibility, (Susser 1991). As described above, biological plausibility is given very low ranking in the 'criteria' for causal inference. At the time of publication of the Hill and US Surgeon General's reports there was lamentably little information on biological plausibility for many inferred cause-and-effect relationships. Advances in the biological sciences now provide more information in this area, although, as discussed below, no definitive mechanisms have yet been proven for smoking and health relationships. Pursuit of such confirmed mechanisms is obviously desirable, but even in the absence of definitive information, some assessment of biologically plausible mechanisms can considerably assist the determination of causal inference (Weed & Hursting 1998).

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The interpretation of evidence on smoking and health:

Public Health:

Both the Hill and the US Surgeon General's reports were specifically intended for assessment of evidence in a public health context. The determination of "causation" utilised in the public health arena must clearly be less rigorous than that used by research scientists investigating mechanisms of disease. In that public health scientists and regulators have protection of the public health as their primary concern, public health intervention can, and must, occur even in the absence of a clear proof of causation. Therefore, evidence from populations (i.e. 'general causation' or 'population based causal inferences') that a particular exposure is likely to be implicated in a particular disease process will often be sufficient to justify some type of action. Currently the term "precautionary principle" is being used to describe the need for public health intervention in the absence of what might be considered a generally accepted demonstration of causation.

From a public health perspective, it is prudent to assume a causal relationship between cigarette smoking and lung cancer and chronic obstructive pulmonary disease. In both of the above cases the epidemiological evidence is strong, and there is some evidence for reasonable biologically plausible mechanisms. However our knowledge of experimental evidence of the relevant agents and the mechanisms involved is clearly still incomplete. Given that the goal of public health is to reduce overall mortality, an understanding of the detailed mechanisms adds little useful information. If a reduction in lung cancer incidence can be achieved by decreasing smoking prevalence then they are justified in recommending such action based on the epidemiology alone. However if one wishes to reduce the risks for those adults who choose to continue to smoke then a deeper understanding of how smoking causes disease is required.

Product development:

To design new products which may offer a reduction in the risks associated with a conventional cigarette, it is necessary to understand what factors within a given product are important for a given disease. While epidemiology can identify the diseases for which smoking may be a "component cause", it cannot typically provide the detailed information needed to specifically guide product development. An understanding of the pathogenesis of the disease and a fundamental understanding of how smoke exposure influences those processes would be most useful in determining the best approaches for changes to the product. Even more directed product development efforts could be devised if this understanding included knowledge of how either specific chemicals or classes of chemicals in smoke influenced the disease process. Typically this information is derived using experimental systems and therefore depends on indirect evidence. Success in terms of an impact on human health then needs to be confirmed using the tools of epidemiology. Through this cycle of epidemiology, laboratory investigations, product changes, and back to epidemiology it may be possible to gain a better understanding of the relevant agents and mechanism(s) of smoking that act as a "component cause" for particular diseases.

Areas for Future Research:

As described above, much is known about the relationship between smoking and various health effects. There remain, however, many areas where further research is necessary. Key areas are; populations susceptible to particular diseases; direct mechanisms of action of cigarette smoke components on health endpoints which would indicate promising routes for product modifications to minimise exposure to such components; and better characterisation of diseases where smoking plays a role.

Susceptible populations:

Constitutive differences between different smokers may explain why some smokers succumb to disease while others do not. There has, for example, been considerable speculation as to the role of some metabolic enzyme polymorphisms in providing some susceptibilities to tobacco smoke induction of lung cancer. However, research efforts so far have failed to consistently confirm the existence of such a genetic susceptibility in any given population.

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Research into susceptible groups would help in providing information on high-risk groups, who perhaps should be more strongly advised against smoking than other groups. (However, care must be taken not to suggest that those not falling within such high-risk groups may smoke without concern for their health!) Arguably more important, information on such susceptibilities will provide information on mechanisms of causation that may ultimately help in designing potentially less harmful products.

Direct mechanisms and characterisation of diseases:

One of the key objectives of PM is the development of potentially reduced harm cigarettes. Currently we have some indications of directions that may be worthwhile following in achieving such a goal. These include reduction of several potentially harmful smoke constituents. It is important to note, and somewhat disappointing, however, that there is no general consensus as to which constituents may be important for health risks from smoking. The list of potential target smoke constituents has largely been based on the known toxicology of these chemicals independent of their properties in the tobacco smoke matrix. Indeed for most of these constituents the level to which a smoker is exposed from smoking cigarettes is generally well below the levels for which such toxicological activity has been observed.

In addition it has been pointed out very elegantly that in many cases "cause" and "definition" are inseparable (Vineis & Porta 1996). As an example, tuberculosis is both caused, and defined by, the bacillus *Mycobacterium tuberculosis.* Such a combination of cause and definition does not exist for smoking. Although highly speculative, let us suppose that cigarette smoking were to cause a specific gene mutation which characterised all lung cancers which were caused by smoking. Ultimately, identification of such a gene mutation could be a marker for a specific type of lung cancer, designated for example as "Cigarette smoke lung cancer". Were such a definitive marker of smoking-induced lung cancer realisable, one could easily identify all people who succumbed to lung cancer directly as a result of smoking. Accurate monitoring of smoking attributable risks, and modifications to such risks on the introduction of new products, could thus be afforded.

Unfortunately, such a simplistic approach would appear to be unrealistic. Nevertheless, attempts have been made along these lines, related to mutations in the p53 gene (e.g. Denissenko et al. 1996). So far not only has no such marker been identified in all lung cancers in smokers, but certainly no such marker has been found which is uniquely found in individuals exposed to tobacco smoke. The former is not necessary; in fact it seems probable that not all lung cancers in smokers are caused directly by tobacco smoke. However, the latter, a marker unique to exposed individuals, is essential in order to qualify as a definitive marker of a smoking-related disease. The situation is rendered even more complicated because "lung cancer" is a rather general term describing a number of different "diseases" – each of which one would expect to be defined differently.

It is virtually unimaginable that such definitive markers will become available for most smoking-related health endpoints, and thus perhaps the scenario painted above is too unlikely to be of any real utility. However, research into further characterisation of smoking-related diseases may prove to have considerable utility without being definitively complete. Such research could, for example, help to identify specific mechanisms.

Research into the mechanism(s) and relevant agents through which smoking may influence various health endpoints should provide us with information on what product modifications are likely to contribute to reduced harm cigarettes. Such research would also provide information for developing tests of the efficacy of such potentially reduced harm cigarettes; through, for example, identification of early markers of disease for molecular epidemiology studies. It should be borne in mind, however, that the mechanim(s) involved may be so complex that a simple product modification may not be apparent.

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(Taken from the report itself) According to the report, in 1995, American Indians/Alaskan Natives reported the highest prevalence of smoking (36.2%) and was lowest among Asian/Pacific islanders (16.6%). Slight difference reported between whites and non-Hispanic Blacks; 2506% and 25.8% respectively. Since 1992, the prevalence of smoking among blacks has been similar to that of whites (30-32). COPD increases sharply with age. Prevalence of the condition is approximately 50% greater in whites than in blacks. Prevalence is similar across all age groups. Overall COPD rates have increased over the years due to the aging of the population. In 1995 the age-adjusted death rate for black men was 326 per 100,000, for white men was 218; 210 for black women; and 125 for white women (Chapter 11, 2); Hispanic women had lower age-adjusted death rates for ischemic heart disease than non-Hispanic women than non-Hispanic women women. Hispanic men had lower mortality rates than non-Hispanic men for both heart disease and stroke. Asian Americans at lower risk but as in all groups CVD causes are the leading contributor to mortality (Chapter 11; 3).

CHD death rates are higher among blacks than whites until advanced age at which point they are higher among whites.Rate for black men higher than that for white men. Black women die at a rate of 1.35 times the rate for white women. Limited data on Hispanics show that age-adjusted CHD death rates are comparable to those of non-Hispanics among women and slighgtly (6%) lower among men. Americans of Asian and Pacific Island origin have age-adjusted CHD mortality rates approximately half that of white americans.

Report indicates cigarette smoke is a major cause of CHD among both men and women. Smokers have twice the risk of heart attack as nonsmokers. Smokers have 2-4 times the risk of sudden death as nonsmokers. Risk increases with number of cigarettes smoked (11;26).

Source: https://www.industrydocuments.ucsf.edu/docs/lfvl0001